

REMARKS/ARGUMENTS

With this amendment, claims 37-48 are pending. For convenience, the Examiner's rejections are addressed in the order presented in an October 2, 2003, Office Action.

I. Status of the claims

Claims 37-48 are pending. Claims 1-36 are canceled without prejudice to subsequent revival.

II. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-3, 5-12, 23-27, 33-35, and 37-48 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification as originally filed. To the extent the rejection applies to the claims as amended, Applicants respectfully traverse the rejection. Claims 1-3, 5-12, 23-27, and 33-35 are cancelled. Claims 37-48, directed to a genus of nucleic acids that encode a fusion polypeptide comprising an enzymatically active α -2,3-sialyltransferase and an enzymatically active CMP-Neu5Ac synthetase are pending. Dependent claims are directed to fusion proteins comprising enzymes derived from bacterial sources and fusion proteins comprising enzymes derived from *Neisseria*.

The rejection focuses on the structural description of the claimed nucleic acids and encoded polypeptides. Applicants assert that such analysis ignores the point of patentability of the invention, *i.e.*, the combination of an accessory enzyme (*e.g.*, a CMP-Neu5Ac synthetase) and a glycosyltransferase (*e.g.*, an α -2,3-sialyltransferase) into a single fusion protein.

United States courts have ruled that claims directed to combinations of known compounds and uses of such combinations require "written description only so specific as to lead one having ordinary skill in the art to that class of compounds." *In re Herschler*, 200 USPQ 711, 718 (CCPA, 1979); *see also In re Fuetterer*, 138 USPQ 217 (CCPA, 1963). Moreover, the written description requirement is met if the application "provides adequate direction which reasonably leads persons skilled in the art to the later claimed compound." *In re Edwards*, 196 USPQ 465, 467 (CCPA, 1978).

The invention is not newly discovered accessory enzymes or newly discovered glycosyltransferases. Rather, the invention lies in the combination of an accessory enzyme and a glycosyltransferase for production of oligosaccharides, *in vitro* or in host cells. The description of the classes of accessory enzymes (e.g., CMP-Neu5Ac synthetases at page 22, line 29 through page 23, line 6) and glycosyltransferases (e.g., α -2,3-sialyltransferases at page 14, lines 14-28 and page 17, lines 3-8) meets the standards of written description for combinations of identified proteins under set forth in *In re Herschler*.

However, Applicants also assert that the specification provides adequate description of at least three species of the claimed fusion proteins. The Office Action alleges that the specification does not disclose even a single species of the claimed genus of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins. According to the MPEP, the specification must convey with "reasonable clarity to those skilled in the art" that the applicant was in possession of the claimed invention as of the filing date. MPEP 2163. In addition, the description need only describe in detail that which is new or not conventional. *See Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986); M.P.E.P. 2163. As outlined below, the specification does convey to one of skill that Applicants were in possession of three species of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins. These three species and other evidence provided by Applicants provide ample support for the claimed genus of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins.

The specification describes construction of three species of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins in Example 1. A cloning strategy, including PCR primers and starting materials are described at page 39 line 31 through page 40 line 16 of the specification. Three active α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins are described at page 43, lines 19-26 of the specification. The declaration of inventor Dr. Warren Wakarchuk (Exhibit A) explains that one of skill would recognize the structure of the α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion protein species based on the disclosure.

Amino acid and nucleic acids components of the fusion proteins are found in references cited in the specification. These references are incorporated by references for all

purposes at page 52, lines 11-12 of the specification. Thus, reliance on these references for exact sequence information is not improper. *See, e.g.*, MPEP 2163.07(b).

In response to the allegation that no species of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion protein is disclosed in the application, Applicants submit that one of skill would recognize the structure of the three α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins disclosed in Example 1 and that the disclosure provides a representative number of species within the claimed genus. However, as evidence of the structure of the claimed genus, Applicants submit as Exhibit B the full nucleic acid and amino acid sequences for the disclosed species. In addition, Applicants submit evidence of two fusion proteins comprising α -2,3-sialyltransferase from *C. jejuni* and CMP-Neu5Ac synthetase from *Neisseria* as Exhibit C. The fusions were made using either the full length *C. jejuni* α -2,3-sialyltransferase (amino acids 1-430) or a truncated version of the *C. jejuni* α -2,3-sialyltransferase (amino acids 1-328) and both fusion proteins were active. Thus, the claimed genus of α -2,3-sialyltransferase/CMP-Neu5Ac synthetase fusion proteins is supported by a representative number of species. In addition, even though the *C. jejuni* α -2,3-sialyltransferase and the *Neisseria* α -2,3-sialyltransferase share little identity at the sequence level, the disclosure also meets the standard of description for a compound set forth in *In re Herschler* and in *In re Edwards*.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, written description, be withdrawn.

III. Rejections under 35 U.S.C. §103(a)

Claims 1-3, 5-12, 23-27, 33-35, and 37-48 are rejected as allegedly unpatentable over various combinations of references. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP §2143. See also *In re*

Rouffet, 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembicza*k, 50 USPQ2d 1614, 1617 (1999).

As argued below, the references cited by the Office Action fail to provide all the elements of the rejected claims. In addition, the references cited by the Office Action and the arguments put forth within the Office Action fail to provide evidence of a clear and particular showing of a motivation to combine the cited references to arrive at the claimed invention.

As amended, the claims are directed to a genus of nucleic acids that encode a fusion polypeptide comprising an enzymatically active α -2,3-sialyltransferase and an enzymatically active CMP-Neu5Ac synthetase. Dependent claims are directed to fusion proteins comprising enzymes derived from bacterial sources and fusion proteins comprising enzymes derived from *Neisseria*.

A. Rejection of claims 1-3, 5-12, 23-27, and 33-35 under 35 U.S.C. §103(a).

Claims 1-3, 5-12, 23-27, and 33-35 are rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of Bulow *et al.*, TIBech 9:226-231 (1991); Defrees *et al.*, WO 96/32491; and the common knowledge of the art of molecular biology provided by Sambrook *et al.*, pages 7.37-7.52 (1989). Claims 1-3, 5-12, 23-27, and 33-35 are canceled. In view of this amendment, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

B. Rejections of claims 37-48 under 35 U.S.C. §103(a).

Claims 37-48 are rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of Bulow *et al.*, Defrees *et al.*, and Sambrook *et al.* in further view of Gilbert(a) *et al.* Eur. J. Biochem., 249:187-194 (1997) and Gilbert(b) *et al.* Biotech. Lett. 19:417-420 (1997). However, as none of the cited references disclose all the elements of the claimed invention and

also fail to provide motivation for combination of the references to arrive at the claimed invention, the rejection should be withdrawn.

Bulow *et al.* disclose a number of fusion proteins, but do not specifically teach the fusion of an α -2,3-sialyltransferase with a CMP-Neu5Ac synthetase. The reference also fails to provide any motivation for that combination.

Defrees *et al.* teach methods of improving the production of sialylated oligosaccharides by using a reaction mix comprising unfused α -2,3-sialyltransferase, a CMP-Neu5Ac synthetase, a CMP regenerating system, and appropriate concentrations of divalent cations. No fusion of an α -2,3-sialyltransferase with a CMP-Neu5Ac synthetase is disclosed and no deficiency in the system that would provide a motivation for improvement by use of fusion proteins is disclosed.

Sambrook *et al.* provide only general cloning protocols and do not disclose or suggest the combination of a α -2,3-sialyltransferase with a CMP-Neu5Ac synthetase.

Gilbert(a) *et al.* teaches the cloning of a recombinant α -2,3-sialyltransferase from *Neisseria* and its expression in *E. coli*, but does not teach or suggest fusion of that enzyme with a CMP-Neu5Ac synthetase enzyme. The reference discloses the donor and acceptor specificity of the enzyme. At page 193 column 1, Gilbert(a) *et al.* states that yields of recombinant α -2,3-sialyltransferase are low, but that purification to homogeneity is not required for preparative synthetic reactions, so large quantities of α -2,3-sialyltransferase can be obtained without extensive purification. Thus, Gilbert(a) *et al.* fails to provide a motivation for improving the yield of products synthesized by the α -2,3-sialyltransferase enzyme.

Gilbert(b) *et al.* teaches expression of and purification of *Neisseria* CMP-Neu5Ac synthetase in *E. coli*. The reference also discloses a coupled reaction containing *Neisseria* α -2,3-sialyltransferase and the CMP-Neu5Ac synthetase that resulted in a high yield of the desired product. However, no fusion of the two enzymes is taught. The CMP-Neu5Ac synthetase enzyme is disclosed to have properties required for use in preparative biosynthesis of sialylated oligosaccharides, even without fusion to an α -2,3-sialyltransferase protein. Thus, Gilbert(b) *et al.* do not suggest the combination of α -2,3-sialyltransferase with a CMP-Neu5Ac synthetase.



Appl. No. 09/211,691
Amdt. dated March 1, 2004
Reply to Office Action of October 2, 2003

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As argued above, none of the cited references, alone or in combination, teach all the elements of the claimed invention. Moreover, none of the cited references, alone or in combination, provide a motivation or suggestion for the combination of references to arrive at the claimed invention. In view of the above amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. §103(a) be withdrawn.

IV. Rejections under 35 U.S.C. §101, statutory double patenting

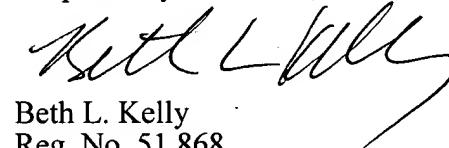
Claims 1-3, 5-12, 23-27, and 33-35 are rejected for alleged double patenting over claims in U.S. Patent Application No. 10/317,723 or U.S. Patent Application No. 10/317,773. To the extent the rejection applies to the amended claims, Applicants respectfully traverse. Claims 1-3, 5-12, 23-27, and 33-35 of the present application are canceled. In view of the above amendment, Applicants respectfully request that the rejection for alleged double patenting be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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